UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, DC 20231

APPLICATION NO.	FILING DAT	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/466,381	06/0[illegible]	ISRAELI R	41426-C/JPW/

HM21/0512

JOHN P WHITE, ESQ.
COOPER & DUNHAM LLP
1185 AVENUE OF THE AMERICAS
NEW YORK NY 10036

EXAMINER	
CAPUTA, A	

ART UNIT	PAPER NUMBER
1645	8

DATE MAILED: 05/12/98

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

☆U.S.GOVERNMENT PRINTING OFFICE 1995-319-826

Office Action Summary	Application No. 08/466,381	Applicant(s) Israeli et al.
	Examiner Anthony C. Caputa	Group Art Unit 1645

☒ Responsive to communication(s) filed on *13 Feb 1998*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *90-93* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *90-93* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *6*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

1. The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1645.

Specification

2. Sequence rules set forth in 37 C.F.R. § 1.821 require the use of SEQ ID No if the sequence is embedded in the text or in the claims. All sequences must be referred to by use of an identifier such as "SEQ ID NO" as presented in the Sequence Listing even though the sequence itself may be imbedded in the text of the application.

The disclosure and/or claims (i.e. Brief Description of Drawings) of the application mention a sequence that is set forth in the Sequence listing but reference is not properly made to the sequence by the use of a sequence identifier in the text.

Claim Rejections - 35 USC § 112

3. **(NEW GROUNDS OF REJECTION)** Claims 90-93 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification provides insufficient guidance of how to use a nucleic molecule of at least 15 nucleotide that hybridize to the nucleic acid molecule as claimed.

The nucleotide sequence of the prostate specific membrane antigen is over 2000 nucleotides and it would be an undue burden to an artisan in the art to determine those molecule(s) of at least 15 nucleotide of that specific hybridize as claimed given that molecules of 15 nucleotide have different sequences and would not have expected to hybridize equally to the claimed molecule. Furthermore, since the specification does not disclose the experimental

parameters used for hybridization it would be an undue burden to identify nucleic acid of at least 15 nucleotide which specifically hybridize to the nucleic acid molecule encoding the specific antigen.

Additionally, the specification provides insufficient guidance to those nucleic acid molecules that encode for modifications (i.e. deletions, or additions) to the PSM, nucleic acid molecules which encodes for a product that has the biological activity, and nucleic acid molecule which hybridize conditions to the DNA as set forth in the claimed invention. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of deletions, additions, or modifications broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. The amino acid sequence of a protein determines its structural and functional properties, and the predictability of which changes can be tolerated in a protein's amino acid sequence and still retain similar activity/utility requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, the problem of predicting protein structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex and well outside the realm of routine experimentation. While recombinant and mutagenesis techniques are known, it is **not** routine in the art to screen for positions within the protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity/utility are limited in any protein and the result of such modifications is unpredictable based on the instant disclosure. One skilled in the art would expect any tolerance to modification shown for a given protein to diminish with each further and additional modification, e.g. multiple deletions. The sequence of some proteins is highly conserved and one skilled in the art would not expect tolerance to any amino acids modification in such proteins. The specification does not support the broad scope of the claims because the specification does **not** disclose the following :

- the general tolerance to modification and extent of such tolerance;
- specific positions and regions of the sequence(s) which can be predictably modified and which regions are critical;
- what fragments, if any, can be made which retain the biological activity of the intact protein; and
- the specification provide essentially no guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have **not** provided sufficient guidance to enable one skilled in the art to make and use the claimed protein in manner reasonably correlated with the scope of the claims broadly including any number of deletions and fragments of any size. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made in the proteins structure and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027, Ex parte Forman, 230 U.S.P.Q. 546 (Bd. Pat. App. & Int. 1986), and Ex parte Anderson, 30 USPQ 2d 1866 (Bd. Pat. App. & Int. 1993).

Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, Kumar et al. teach amino acid variation at a single residue can affect the properties of the function of a peptide. Bowie et al. teach at certain positions of a protein, no substitutions or only conservative substitutions are allowed. In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduce the biological activity of the mitogen (see Lazar et al.). These references demonstrates that a even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein. In view of the lack of guidance, lack of examples, and lack of predictability associated with regard to producing and using the myriad of derivatives of DNA which encode for a protein (or polypeptide, peptide) encompassed in the scope of the claims one

skilled in the art would be forced into undue experimentation in order to practice broadly the claimed invention.

Additionally, the specification provide insufficient guidance of how to use a "primer" or "molecule of at least 15 nucleotides" for "detecting micrometastic tumors" as broadly recited.

Since:

1) the claimed "primer" and "molecule of at least 15 nucleotides" is not limited to any "sequence";

2) the claimed "primer" is no limited to any size;

3) the art as exemplified by US Patent No. 5,538,866 only sets forth "For prostatic cancer, the PSM antigen probe may prove beneficial" (see Column 21, lines 50-59); and

4) the art as exemplified by Fey et al. (Eur. J. Cancer 27(1):89-94 1991) sets forth that "Although PCR holds great promise for "molecular" staging and follow-up, several technical problems have to be kept in mind, and the clinical relevance of PCR-based evidence of minimal residual disease in haematological malignancies requires further investigation"

a skilled artisan would be forced into undue experimentation to practice the claimed invention.

4. The prior rejection of claims 90-93 under 35 U.S.C. 112, first paragraph, for written description is withdrawn in view of applicants amendment.

5. **(NEW GROUNDS OF REJECTION)** Claims 90-93 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 90-93 are rejected for using the phrase "specifically hybridizing" since it is not clear what conditions constitute as "specifically hybridizing".

6. Any inquiry concerning this communication should be directed to Dr. Anthony C. Caputa, whose telephone number is 703-308-3995.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is 703-308-0196.

Papers related to this application may be submitted to Art Unit 1645 by facsimile transmission. Papers should be faxed to Art Unit 1645 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the official Gazette 1096 OG 30 (November 15, 1989). The CMI Fax Center number is (703)-308-4242.

Anthony C. Caputa, Ph.D.
May 10, 1998

ANTHONY C. CAPUTA
PRIMARY EXAMINER